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**TELEFAX**

Date: December 9, 2008 Total pages: 34 incl. cover sheet  
To: USPTO Telephone: Telefax: 571 273 8300  
From: Michael J. Terapane, J.D., Ph.D. Telephone: 404-879-2155 Telefax: 404-879-2160  
Our Docket No. ACU 109 CIP Client/Matter No. 077586-00027  
Your Docket No.

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**MESSAGE:**

**IN THE UNITED STATES PATENT AND TRADEMARK OFFICE**

Applicants: Julie Straub, David Altreuter, Howard Bernstein, Donald E. Chickering, III,  
Sarwat Khattak, and Greg Randall

Serial No.: 10/053,929 Art Unit: 1618

Filed: January 22, 2002 Examiner: Blessing M. Fubara

For: *POROUS DRUG MATRICES AND METHODS OF MANUFACTURE THEREOF*

**ATTACHMENT:**

Transmittal Form - PTO/SB/21;  
Fee Transmittal Form - PTO/SB/17;  
Appeal Brief, along with two (2) References

{45093480.1}

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077586-00027

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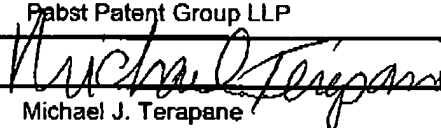
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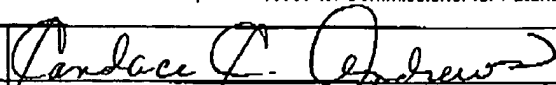
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<b>TRANSMITTAL FORM</b>  (to be used for all correspondence after initial filing)	Application Number	10/053,929
	Filing Date	January 22, 2002
	First Named Inventor	Julie Straub
	Art Unit	1618
	Examiner Name	Blessing M. Fubara
Total Number of Pages in This Submission	Attorney Docket Number	ACU 109 CIP

ENCLOSURES (Check all that apply)		
<input checked="" type="checkbox"/> Fee Transmittal Form <input type="checkbox"/> Fee Attached <input type="checkbox"/> Amendment/Reply <input type="checkbox"/> After Final <input type="checkbox"/> Affidavits/declaration(s) <input type="checkbox"/> Extension of Time Request <input type="checkbox"/> Express Abandonment Request <input type="checkbox"/> Information Disclosure Statement <input type="checkbox"/> Certified Copy of Priority Document(s) <input type="checkbox"/> Reply to Missing Parts/ Incomplete Application <input type="checkbox"/> Reply to Missing Parts under 37 CFR 1.52 or 1.53	<input type="checkbox"/> Drawing(s) <input type="checkbox"/> Licensing-related Papers <input type="checkbox"/> Petition <input type="checkbox"/> Petition to Convert to a Provisional Application <input type="checkbox"/> Power of Attorney, Revocation Change of Correspondence Address <input type="checkbox"/> Terminal Disclaimer <input type="checkbox"/> Request for Refund <input type="checkbox"/> CD, Number of CD(s) _____ <input type="checkbox"/> Landscape Table on CD	<input type="checkbox"/> After Allowance Communication to TC <input type="checkbox"/> Appeal Communication to Board of Appeals and Interferences <input checked="" type="checkbox"/> Appeal Communication to TC (Appeal Notice, Brief, Reply Brief) <input type="checkbox"/> Proprietary Information <input type="checkbox"/> Status Letter <input checked="" type="checkbox"/> Other Enclosure(s) (please identify below): 1. MSDS PEG Telomer B.; and 2. Definition of "Volatile"
Remarks		

SIGNATURE OF APPLICANT, ATTORNEY, OR AGENT			
Firm Name	Pabst Patent Group LLP		
Signature			
Printed name	Michael J. Terapane		
Date	December 9, 2008	Reg. No.	57,633

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Signature			
Typed or printed name	Candace C. Andrews	Date	December 9, 2008

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**FEE TRANSMITTAL**  
**For FY 2009**☐ Applicant claims small entity status. See 37 CFR 1.27

TOTAL AMOUNT OF PAYMENT (\$) \$40.00

**Complete if Known**

Application Number	10/053,929
Filing Date	January 22, 2002
First Named Inventor	Julie Straub
Examiner Name	Blessing M. Fubara
Art Unit	1618
Attorney Docket No.	ACU 109 CIP

**METHOD OF PAYMENT (check all that apply)**☐ Check ☐ Credit Card ☐ Money Order ☐ None ☐ Other (please identify): \_\_\_\_\_☒ Deposit Account Deposit Account Number: 50-3129 Deposit Account Name: \_\_\_\_\_

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☒ Charge fee(s) indicated below ☐ Charge fee(s) indicated below, except for the filing fee☒ Charge any additional fee(s) or underpayments of fee(s) under 37 CFR 1.16 and 1.17 ☐ Credit any overpayments

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**FEE CALCULATION****1. BASIC FILING, SEARCH, AND EXAMINATION FEES**

Application Type	FILING FEES		SEARCH FEES		EXAMINATION FEES		Fees Paid (\$)
	Fee (\$)	Small Entity Fee (\$)	Fee (\$)	Small Entity Fee (\$)	Fee (\$)	Small Entity Fee (\$)	
Utility	330	165	540	270	220	110	
Design	220	110	100	50	140	70	
Plant	220	110	330	165	170	85	
Reissue	330	165	540	270	650	325	
Provisional	220	110	0	0	0	0	

**2. EXCESS CLAIM FEES****Fee Description**

Each claim over 20 (including Reissues)

Fee (\$)	Small Entity Fee (\$)
52	26

Each independent claim over 3 (including Reissues)

220	110
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Multiple dependent claims

390	195
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Total Claims	Extra Claims	Fee (\$)	Fee Paid (\$)
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- 20 or HP =	x	=	
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HP = highest number of total claims paid for, if greater than 20.

Indep. Claims	Extra Claims	Fee (\$)	Fee Paid (\$)
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- 3 or HP =	x	=	
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HP = highest number of independent claims paid for, if greater than 3.

**3. APPLICATION SIZE FEE**

If the specification and drawings exceed 100 sheets of paper (excluding electronically filed sequence or computer listings under 37 CFR 1.52(e)), the application size fee due is \$270 (\$135 for small entity) for each additional 50 sheets or fraction thereof. See 35 U.S.C. 41(a)(1)(G) and 37 CFR 1.16(s).

Total Sheets	Extra Sheets	Number of each additional 50 or fraction thereof	Fee (\$)	Fee Paid (\$)
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- 100 =	/ 50 =	(round up to a whole number) x	=	
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**4. OTHER FEE(S)**

Non-English Specification, \$130 fee (no small entity discount)

Fees Paid (\$)

Other (e.g., late filing surcharge) - Appeal Brief - The Appeal Brief fee (\$500) was previously paid on July 9, 2007, therefore, leaving a balance of \$40

40.00

**SUBMITTED BY**

Signature	<i>Michael J. Terapane</i>	Registration No. (Attorney/Agent)	57,833	Telephone	404-879-2155
Name (Print/Type)	Michael J. Terapane, J.D., Ph.D.	Date	December 9, 2008		

This collection of information is required by 37 CFR 1.136. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 30 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. SEND TO: Commissioner for Patents, P.O. Box 1460, Alexandria, VA 22313-1460.

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## IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

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Applicants: Julie Straub, David Altreuter, Howard Bernstein, Donald E. Chickering, III, DEC - 9 2008  
Sarwat Khattak, and Greg Randall

Serial No.: 10/053,929

Art Unit: 1618

Filed: January 22, 2002

Examiner: Blessing M. Fubara

For: *POROUS DRUG MATRICES AND METHODS OF MANUFACTURE THEREOF*

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Commissioner for Patents  
P.O. Box 1450  
Alexandria, VA 22313-1450

**APPEAL BRIEF**

Sir:

This is an appeal from the final rejection of claims 16-21 and 34 in the Office Action mailed October 16, 2008 in the above-identified patent application. A first Notice of Appeal was filed on April 9, 2007. A second Notice of Appeal was filed on December 8, 2008. A terminal disclaimer was filed on December 8, 2008.

A first Appeal Brief was filed on July 9, 2007. The fee for an Appeal Brief was previously paid on July 9, 2007. The fee for an Appeal Brief has since increased from \$500 to \$540. The Commissioner is hereby authorized to charge \$40, the difference between the fee for an Appeal Brief that was previously paid and the current fee for a large entity, to Deposit Account No. 50-3129.

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Adjustment date: 12/10/2008 JYONG1  
07710/2007 INTEFSW 00000617 503129 10053929  
01 FC:1402 500.00 CR

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It is believed that no additional fee is required with this submission. However, should an additional fee be required, the Commissioner is hereby authorized to charge the fee to Deposit Account No. 50-3129.

**(1) REAL PARTIES IN INTEREST**

The real parties in interest of this application are Acusphere, Inc., the assignee, and Cephalon, Inc., the licensee.

**(2) RELATED APPEALS AND INTERFERENCES**

There are no related appeals or interferences.

**(3) STATUS OF CLAIMS**

Claims 16-21 and 34 are pending. Claims 1-15 and 22-33 have been cancelled. Claims 16-21 and 34 are on appeal. The text of each claim on appeal, as pending, is set forth in an Appendix to this Appeal Brief.

**(4) STATUS OF AMENDMENTS**

Responses after final rejection were filed on March 6, 2007 and June 25, 2007. The claims were not amended after final rejection. The claims were last amended in an Amendment filed September 18, 2006. An appendix sets forth the claims on appeal.

**(5) SUMMARY OF CLAIMED SUBJECT MATTER**

Independent claim 16 defines a method for making a pharmaceutical composition comprising a porous matrix formed of at least one hydrophilic or hydrophobic excipient and microparticles of a drug, wherein the microparticles have a mean diameter between about 0.1 and 5  $\mu\text{m}$  and a total surface area greater than about 0.5  $\text{m}^2/\text{mL}$ , and wherein the dry porous matrix is

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in a dry powder form having a TAP density less than or equal to 1.0 g/mL and having a total surface area of greater than or equal to 0.2 m<sup>2</sup>/g. Claim 16 requires the following steps: (a) dissolving a drug in a volatile solvent to form a drug solution, (b) combining at least one volatile solid pore forming agent with the drug solution to form an emulsion, suspension, or second solution, (c) incorporating at least one excipient into the emulsion, suspension, or second solution, wherein the excipient is selected from the group consisting of hydrophobic and hydrophilic excipients which enhance dissolution rate, which stabilize drug in amorphous form by preventing crystallization, and which stabilize drug in crystalline form by inhibiting crystal growth, and (d) removing the volatile solvent and pore forming agent from the emulsion, suspension, or second solution to yield the porous matrix of drug and excipient (page 3, lines 14-25; and page 4, lines 2-5).

Dependent claim 17 specifies that the volatile solvent can be removed using a technique chosen from spray drying, evaporation, fluid bed drying, lyophilization, vacuum drying, or a combination thereof (page 22, lines 5-8).

Dependent claim 18 specifies that the excipients may be polymers, amino acids, wetting agents, sugars, preservatives, pegylated excipients, tonicity agents, or combinations thereof (page 13, line 8 to page 19, line 18).

Dependent claim 20 specifies that the pore forming agent may be a volatile salt (page 19, lines 21-22). Dependent claim 21 further specifies that the volatile salt may be ammonium bicarbonate, ammonium acetate, ammonium chloride, ammonium benzoate, and mixtures thereof (page 20, lines 28-30).

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Dependent claim 19 specifies that the matrix contains between 1 and 95% drug by weight in combination with at least one hydrophilic or hydrophobic excipient which enhances the rate of drug dissolution, stabilizes the drug in crystalline form by inhibiting crystal growth or stabilizes the drug in amorphous form by preventing crystallization (page 6, lines 2-6 and page 4, lines 5-9).

Dependent claim 34 specifies that the drug may be an analgesic or antipyretic, antiasthmatic, anti-inflammatory, antimigraine agent, antiarthritic agent, anticonvulsant, antibacterial agent, antiviral agent, or antimicrobial (page 7, line 5 to page 11, line 27).

**(6) GROUNDS OF REJECTION TO BE REVIEWED ON APPEAL**

The sole issue presented on appeal is:

(1) whether claims 16-21 and 34 are non-obvious as required by 35 U.S.C. § 103(a) over U.S. Patent Application Publication No. 2001/0018072 to Unger ("Unger").

**(7) ARGUMENT**

**(i) Rejections Under 35 U.S.C. § 103**

*Legal Standard*

The starting point for an analysis under 35 U.S.C. § 103(a) is the Supreme Court's decision in *KSR International Co. v. Teleflex, Inc.*, 127 S. Ct. 1727, 82 U.S.P.Q.2d 1385 (2007), which refocused the determination of whether a claimed invention is obvious back to the process the Court had defined in *Graham v. John Deere Co.*, 383 U.S. 1, 17-18, 148 U.S.P.Q. 459, 467 (1966). There, the Court had held that the obviousness determination should address four factors, all of which must be considered, though not in any prescribed order:

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- (1) the scope and content of the prior art;
- (2) the level of ordinary skill in the art;
- (3) the differences between the claimed invention and the prior art; and

(4) any secondary considerations suggesting nonobviousness, such as commercial success, failure of others, and long felt but unmet need. *Id.* The Court cautioned that the fact finder should be careful about reading the teachings of the invention at issue into the prior art, to avoid applying inappropriate hindsight, *ex post* reasoning. *Id.* at 36.

In *KSR*, the Court reversed a decision of the Federal Circuit that it characterized as having applied too mechanistically the role of “teaching, suggestion, motivation” (“TSM”) in the prior art to combine references, to the exclusion of any consideration of other factors, such as the general knowledge and creativity of a person of ordinary skill in the art, or the competitive pressures to solve the problem addressed by the invention, that may provide the motivation to combine elements. 127 S. Ct. at 1739-43. The Court explained that TSM should not be abandoned, however consideration of other evidence relevant to whether it would have been obvious to combine prior art to achieve the result claimed by the inventors must also be considered.

The Court also warned against the use of hindsight analysis in making an obviousness determination. The Court stated, “A factfinder should be aware, of course, of the distortion caused by hindsight bias and must be cautious of arguments reliant upon *ex post* reasoning.” *KSR*, 127 S. Ct. at 1742, citing *Graham*, 383 U.S. at 36 (warning against a “temptation to read into the prior art the teachings of the invention in issue” and instructing courts to “guard against

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slipping into the use of hindsight” (quoting *Monroe Auto Equipment Co. v. Heckethorn Mfg. & Supply Co.*, 332 F.2d 406, 412, 141 U.S.P.Q. 549 (6<sup>th</sup> Cir. 1964))).

Analysis

The *Graham* factors are analyzed below.

(a) *Determining the scope and contents of the prior art*

The scope and contents of the prior art must be made *at the time the invention was made*. The requirement “at the time the invention was made” is to avoid impermissible hindsight. “It is difficult but necessary that the decision maker forget what he or she has been taught [...] about the claimed invention and cast the mind back to the time the invention was made (often as here many years), to occupy the mind of one skilled in the art who is presented only with the references, and who is normally guided by the then-accepted wisdom in the art.” *W.L. Gore & Associates, Inc. v. Garlock, Inc.*, 721 F.2d 1540, 220 U.S.P.Q. 303, 313 (Fed. Cir. 1983).

Unger describes a solid porous matrix containing a surfactant in combination with a bioactive agent (page 1, paragraph 0013). The matrix may be prepared by (1) combining a surfactant and a therapeutic, together with a solvent, to form an emulsion containing random aggregates of the surfactant and the therapeutic, and (2) processing the emulsion by controlled drying, or controlled agitation and controlled drying to form the solid porous matrix (abstract and page 1, paragraph 0014).

Unger is concerned with the targeted delivery of therapeutics to a particular region of patient (page 1, paragraph 0002). The compositions described in Unger may contain a stabilizing material, which is capable of improving the stability of the vesicles (e.g., liposomes,

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lipospheres, particles, etc.) containing gases, gaseous precursors, steroid prodrugs, targeting ligands, and/or other bioactive agents (page 2, paragraph 0031). The stabilizing material can be used to prevent the escape of gases, gaseous precursors, steroid prodrugs, targeting ligands, and/or other bioactive agents.

**(b) *Ascertaining the differences between the prior art and the claims***

In determining the differences between the prior art and the claims, the question under 35 U.S.C. § 103 is not whether the differences themselves would have been obvious, but whether the claimed invention as a whole would have been obvious. *Stratoflex, Inc. v. Aeroquip Corp.*, 713 F.2d 1530, 218 USPQ 871 (Fed. Cir. 1983); *Schenck v. Nortron Corp.*, 713 F.2d 782, 218 U.S.P.Q. 698 (Fed. Cir. 1983).

***The Claimed method***

The claims define a method for making porous drug matrices. As discussed in the specification, such drug matrices are particularly useful for increasing the dissolution rates for drugs, especially drugs with low aqueous solubility (*see* page 2, lines 23-27). The matrices contain at least one excipient which enhances the dissolution rate of the drug, stabilizes the drug in an amorphous form by preventing crystallization, or stabilizes the drug in crystalline form by inhibiting crystal growth.

Independent claim 16 and its dependent claims, claims 17-21 and 34, define methods for making a pharmaceutical composition that contains a porous matrix formed of at least one hydrophilic or hydrophobic excipient and microparticles of a drug. As specified in claim 16, the method requires the following steps:

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- (a) dissolving a drug in a volatile solvent to form a drug solution,
- (b) combining at least one volatile solid pore forming agent with the drug solution to form an emulsion, suspension, or second solution,
- (c) incorporating at least one excipient into the emulsion, suspension, or second solution, wherein the excipient is selected from the group consisting of hydrophobic and hydrophilic excipients which enhance dissolution rate, which stabilize drug in amorphous form by preventing crystallization, and which stabilize drug in crystalline form by inhibiting crystal growth, and
- (d) removing the volatile solvent and pore forming agent from the emulsion, suspension, or second solution to yield the porous matrix of drug and excipient.

Independent claim 16 also specifies physical properties of the composition produced by this method. The resulting composition contains microparticles of drug that have a mean diameter between about 0.1 and 5  $\mu\text{m}$  and a total surface area greater than about 0.5  $\text{m}^2/\text{mL}$ . Additionally the composition contains a dry porous matrix in a dry powder form, which has a TAP density of less than or equal to 1.0  $\text{g/mL}$  and a total surface area of greater than or equal to 0.2  $\text{m}^2/\text{g}$ .

As discussed in detail below, Unger describes a different method and different compositions are produced using Unger's method.

**Unger does not disclose or suggest elements (a), (b), (c), and (d) of claim 16**

***Unger does not disclose forming a drug solution***

The Examiner alleges that steps a-c in claim 16 read on the method disclosed in Unger.

(Office Action mailed October 16, 2008, page 3, paragraph 4, lines 8-10). Applicants

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respectfully disagree. As discussed in the Reply Brief dated December 18, 2007 (*see* pages 2 and 3), Unger describes a method for preparing a solid porous matrix (abstract). The matrix is prepared by combining a surfactant and a therapeutic, together with a solvent, to form an emulsion containing random aggregates of the surfactant and the therapeutic, and processing the emulsion to form the matrix (abstract and paragraph 0014). Unger discloses that "[T]he solvent is a **suspending medium** for associating the surfactant with the therapeutic in the preparation of a solid porous matrix. The therapeutic is typically only marginally soluble in the solvent." (paragraph 0075, *emphasis added*). In contrast, the claimed method requires that the active agent be dissolved in a volatile solvent to form a drug solution. A suspension is not a solution.

Unger teaches away from the claimed methods. A reference may be said to teach away when a person of ordinary skill, upon reading the reference, would be discouraged from following the path set out in the reference, or would be led in a direction divergent from the path that was taken by the applicant. The degree of teaching away will of course depend on the particular facts; in general, a reference will teach away if it suggests that the line of development flowing from the reference's disclosure is unlikely to be productive of the result sought by the applicant. *In re Caldwell*, 50 C.C.P.A. 1464, 319 F.2d 254, 256, 138 U.S.P.Q. 243, 245 (CCPA 1963) (reference teaches away if it leaves the impression that the product would not have the property sought by the applicant).

One of ordinary skill in the art, reading Unger, would be led in a direction divergent from the path taken by Appellants. Specifically, one of ordinary skill in the art, reading Unger, would be led to prepare a suspension or emulsion of the active agent, not a solution as defined by claim

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16. Accordingly claims 16-21 and 34 are not obvious over Unger. Applicants note that the Examiner did not address this argument in the Office Action mailed October 16, 2008.

*Gordon teaches away from the method described in Unger*

The Examiner alleges that the specific steps for the production of a powder formulation are known in the art. (Office Action mailed October 16, 2008, page 4, lines 4-9). The Examiner relies on U.S. Patent No. 5,976,574 to Gordon ("Gordon") to support this allegation. (*Id.*). However, the Examiner cannot merely pick and choose steps from different references to arrive at the claimed method. This is improper hindsight analysis. (MPEP 2142).

Gordon describes preparing a drug powder by dissolving a hydrophobic drug in a solvent to form a solution, suspending a hydrophilic excipient in the solution, and then spray drying the solution to form particles (col. 4, lines 12-17). Gordon's method requires different steps than Unger's. Specifically, Unger clearly discloses that the active agent is suspended in the solvent, not dissolved. Therefore, one of ordinary skill in the art could not take steps from Gordon and merely substitute them into Unger's method. In particular, Unger teaches away from such a substitution. Unger states "[T]he therapeutic is typically only marginally soluble in the solvent." (Unger, paragraph 0075). Unger discloses that the drug is suspended in a solvent to form a suspension or an emulsion. Thus, Unger clearly teaches away from the methods described in Gordon. Therefore, one of ordinary skill in the art would not be motivated to combine Unger and Gordon to arrive at the claimed methods.

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***Unger does not disclose or suggest adding a volatile solid pore forming agent to the drug solution and then removing the volatile solid pore forming agent***

Unger describes the use of gases or gaseous precursors, which are entrapped within the matrix (page 20, paragraph 0160 to page 22, paragraph 0175). Unger alleges that the entrapped gas provides the solid porous matrix with enhanced reflectivity (page 20, paragraph 0160). The gas and/or gaseous precursors are not "pore forming agents" nor are they removed from the matrix, as required by the claims on Appeal.

Unger also describes the optional use of gaseous precursors as a solvent (page 20, paragraph 0161). However, this disclosure is specifically in regard to gaseous precursors that are used as a solvent in the preparation of a solid porous matrix. Thus, in these embodiments, Unger's method does not also require first dissolving a drug in a volatile solvent to form a drug solution, and then combining at least one volatile solid pore forming agent with the drug solution to form an emulsion, suspension, or second solution, as specified in the claims on Appeal. Further, none of Unger's examples describe adding a volatile solid pore-forming agent to a drug solution to form a suspension, emulsion, or second solution and then removing the volatile solid pore forming agent to form a porous matrix.

The pores in Unger's compositions are formed by the addition of a blowing agent, methylene chloride, which is a volatile liquid. Unger discloses that in the case of spray drying, "the emulsion or colloidal suspension is placed into association with a blowing agent, such as methylene chloride. As the suspension or emulsion is then spray dried, the drug dries and the

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blowing agent and solvent are removed tending to form microcavities within the drug crystals.”  
(paragraph 0184).

The use of a blowing agent, such as methylene chloride, rather than a volatile solid pore forming agent, is supported by the disclosure in paragraph 0013 of Unger that “the composition optionally contains a gas or gaseous precursor”. The fact that this component is optional is evidence the gas or gaseous precursor is not used as a pore forming agent. The Examiner herself notes the optional use of a gas or gaseous precursor in Unger in the Examiner's Answer mailed on October 18, 2007 (*see* page 4, paragraph (a), line 18).

Further, Gordon does not provide the elements missing from Unger. Gordon discloses suspending a hydrophilic component in a solution of hydrophobic drug (col. 4, lines 12-17). Gordon does disclose or suggest combining at least one volatile solid pore forming agent with the drug solution to form an emulsion, suspension, or second solution. Gordon defines “hydrophilic component” as a component which is highly soluble in water and frequently capable of swelling and forming reversible gels (col. 5, lines 36-38). Gordon goes on to state that excipients will generally be selected to provide stability, dispersibility, consistency, and/or bulking characteristics (col. 5, lines 41-44). None of the hydrophilic excipients listed in Gordon are volatile solid pore forming agents. The definition of “volatile” is enclosed. Gordon does not cure the deficiencies of Unger.

***The Examiner's reliance on example 1 in Unger is not clear***

The Examiner concedes that Unger does not explicitly disclose the claimed method steps in claim 16 (Office Action mailed October 16, 2008, page 4, line 2). The Examiner goes on to

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cite Example 1 in Unger. It is not clear to the undersigned why the Examiner refers to Example 1. However, the Examiner has previously relied on Example 1 as support for the obviousness rejection over Unger.

As discussed previously, such as in the Reply to Examiner's Answer filed on December 18, 2007, Example 1 in Unger describes the encapsulation of dexamethasone in PEG Telomer B, which is a surfactant (page 41, paragraph 0334). Dexamethasone and PEG Telomer B are mixed together and dissolved in methanol and the methanol is removed to form a dried film (*Id.*). PEG Telomer B is **not** a volatile pore forming agent, and PEG Telomer B is **not** removed from the mixture (*Id.*). The film is reconstituted in deionized water to form a homogeneous suspension (*Id.*). There is no indication that the particles in suspension are porous. Example 1 is a prophetic example (page 41, paragraph 0333). It is included to allegedly show the high payload efficiency of the fluorosurfactant technique. There is no teaching or suggestion in Example 1 to include a volatile pore forming agent, let alone a volatile solid pore forming agent.

Further, even if one could argue that PEG Telomer B is a volatile pore forming agent, it is not a volatile solid pore forming agent. PEG Telomer B is a liquid having a boiling point of 200°C (*see* the enclosed Material Safety Data Sheet for PEG Telomer B, originally submitted with Response filed June 25, 2007, a copy of which is enclosed). Example 1 does not disclose the addition of a volatile solid pore forming agent to a drug solution, as required by step (b) of claim 16. Further, Example 1 does not disclose removing the volatile solvent and pore forming agent from the emulsion, suspension, or second solution to yield the porous matrix of drug and excipient as required by step (d) of claim 16.

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***Unger does not disclose compositions containing an excipient which enhances the dissolution rate of the drug, stabilizes the drug in an amorphous form by preventing crystallization, or stabilizes the drug in crystalline form by inhibiting crystal growth***

As discussed above, Unger discloses the use of a stabilizing material (page 2, paragraph 0031). However, Unger's stabilizing material is used to stabilize the vesicle containing the active agent and/or to prevent escape of the gases, gaseous precursors, or bioactive agents. Stabilizing the vesicle is not the equivalent of enhancing the dissolution rate of the drug, stabilizing the drug in an amorphous form by preventing crystallization, or stabilizing the drug in crystalline form by inhibiting crystal growth. Thus, Unger does not disclose or suggest the use of at least one excipient which enhances the dissolution rate of the drug, stabilizes the drug in an amorphous form by preventing crystallization, or stabilizes the drug in crystalline form by inhibiting crystal growth. The Examiner failed to address the absence of this limitation in Unger in the final office action mailed October 16, 2008.

**Unger does not disclose or suggest microparticles with the properties required by claim 16**

Claim 16 specifies the properties of the compositions formed using the claimed method. Unger does not disclose or suggest that the microparticles formed using the process described therein have the properties specified by claim 16. The Examiner failed to address the absence of this limitation in Unger in the final office action mailed October 16, 2008.

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As discussed above, Appellants have distinguished the claimed methods from the methods described in Unger. Therefore, the Examiner cannot argue that the properties defined in claim 16 are inherent.

Moreover, the fact that a certain result or characteristic may occur or be present in the prior art is not sufficient to establish the inherency of that result or characteristic. *In re Rijckaert*, 9 F.3d 1531, 1534, 28 USPQ2d 1955, 1957 (Fed. Cir. 1993) (reversed rejection because inherency was based on what would result due to optimization of conditions, not what was necessarily present in the prior art); *In re Oelrich*, 666 F.2d 578, 581-82, 212 USPQ 323, 326 (CCPA 1981). "To establish inherency, the extrinsic evidence 'must make clear that the missing descriptive matter is necessarily present in the thing described in the reference, and that it would be so recognized by persons of ordinary skill. Inherency, however, may not be established by probabilities or possibilities. The mere fact that a certain thing may result from a given set of circumstances is not sufficient.' " *In re Robertson*, 169 F.3d 743, 745, 49 USPQ2d 1949, 1950-51 (Fed. Cir. 1999) (citations omitted).

"In relying upon the theory of inherency, the examiner must provide a basis in fact and/or technical reasoning to reasonably support the determination that the allegedly inherent characteristic necessarily flows from the teachings of the applied prior art." *Ex parte Levy*, 17 USPQ2d 1461, 1464 (Bd. Pat. App. & Inter. 1990) (emphasis in original). The Examiner has failed to provide a basis in fact and/or technical reasoning to reasonably support the determination that the parameters of the particles specified in claim 16 flow from the teachings

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of Unger, particularly in view of the Examiner's admission that the Unger does not disclose the claimed method steps in the order specified in claim 16.

**The Examiner has failed to establish a *prima facie* case of obviousness**

The Examiner alleged that the Appellants have failed to demonstrate that the claimed method steps, in the exact order, provide unexpected results. (Office Action mailed October 16, 2008, page 4, lines 4 to 5). Unexpected or unpredictable results can be used to rebut a *prima facie* case of obviousness. However, the Examiner has failed to establish a *prima facie* case of obviousness over Unger for at least the reasons discussed above. As noted above, Gordan does not cure the deficiencies of Unger. Accordingly, claims 16-21 and 34 are not obvious over Unger, alone, or in combination with Gordan.

*Claim 18 is not obvious in view of Unger*

In addition to the arguments provided above with respect to claim 16 and its dependent claims, claim 18 is not obvious because Unger does not disclose or suggest the excipients listed in claim 18 to enhance the dissolution rate of the drug, stabilize the drug in an amorphous form by preventing crystallization, or stabilize the drug in crystalline form by inhibiting crystal growth. For at least the reasons discussed above, claim 18 is not obvious over Unger.

*Claims 19 and 20 are not obvious in view of Unger*

In addition to the arguments presented above with respect to claim 16 and its dependent claims, claims 19 and 20 are not obvious because Unger does not disclose or suggest the use of volatile salts as pore forming agents. Unger does not disclose or suggest the use of volatile salts

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as solid pore forming agents, let alone the specific salts listed in claim 20. For at least the reasons discussed above, claims 19 and 20 are not obvious over Unger.

**(c) *Resolving the level of ordinary skill in the art***

The Examiner did not consider this factor in the final office action mailed on October 16, 2008. However, Appellants note that one of ordinary skill in the art at the time of the earliest priority date would likely have a bachelor's or master's degree in chemistry, chemical engineering, or pharmaceuticals with at least approximately five years experience, or a Ph.D. in chemistry, chemical engineering, or pharmaceuticals with at least approximately three years experience.

**(d) *Evaluating evidence of secondary considerations***

Secondary considerations to be considered include commercial success, long felt but unresolved needs, failure of others, etc. *KSR v. Teleflex*, 550 U.S. 398 (2007) citing *Graham v. John Deere Co. of Kansas City*, 383 U.S. 1, 17-18 (1966).

The claims are drawn to methods of making pharmaceutical compositions. These methods are particularly useful for formulating pharmaceutical compositions containing drugs having low solubility. As discussed in the specification, the bioavailability of a drug can be limited by poor dissolution of the drug into aqueous bodily fluids following administration (page 1, lines 17-18). This rate-limiting step can be critical to rapidly attaining therapeutically effective drug levels (page 1, lines 18-20).

Traditional approaches to parenteral delivery of poorly soluble drugs include using large volumes of aqueous diluents, solubilizing agents, detergents, non-aqueous solvents, or non-

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physiological pH solutions (page 1, lines 20-23). These formulations, however, can increase the systemic toxicity of the drug composition or damage tissues the site of administration (page 1, lines 23-25).

Other approaches disclosed in the prior art have focused on the physical form of the drug itself. For example, drugs have been prepared in nanoparticulate form. Nanoparticles, however, can be difficult to produce and maintain in a stable form due to their tendency to flocculate or agglomerate, particularly in the absence of surface modifying agents absorbed or coated onto the particles (page 1, line 31 to page 2, line 3). Further, techniques used for nanonization are typically undesirable due to: (1) the time it takes to process a single batch (e.g., several days); (2) scale up of such techniques can be difficult and costly; and (3) the process can be difficult to conduct aseptically (page 2, lines 3-8). Thus, at the time of the priority application, there existed an unmet need for formulations containing poorly soluble drugs which exhibit increased dissolution of the drug.

Additionally, the claimed methods are quite versatile and are generally useful for increasing the dissolution rates of drugs.

Application of the *Graham* factors demonstrates that one of ordinary skill in the art would not have been motivated to modify Unger to arrive at the claimed methods. Unger is concerned with targeted drug delivery, not formulating poorly soluble drugs to have enhanced dissolution *in vivo*. Unger describes the use of stabilizing materials to stabilize the vesicle containing the active agent, not to enhance dissolution or prevent crystallization of the drug as required by claim 16. Unger does not disclose or suggest steps (a), (b), (c), and (d) of claim 16.

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Unger does not disclose or suggest microparticles having the properties defined in claim 16. One of ordinary skill in the art would not be motivated to modify Unger to arrive at the claimed methods. Therefore claims 16-21 and 34 are not obvious in view of Unger.


**(8) SUMMARY AND CONCLUSION**

Unger does not disclose or suggest a method for making microparticles comprising forming a drug solution, adding a volatile solid pore forming agent to the drug solution to form a suspension, emulsion, or second solution, and removing the pore forming agent to form a porous matrix as required by claim 16. Unger does not disclose or suggest that the microparticles formed using its process have the properties required by claim 16. Unger does not disclose or suggest every element of the claims. Further, the Examiner has provided no reason why one of ordinary skill in the art would be motivated to modify Unger to arrive at the claimed methods. Accordingly, the Examiner has failed to establish a *prima facie* case of obviousness.

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For at least the foregoing reasons, Appellant submits that claims 16-21 and 34 are patentable.

Respectfully submitted,

  
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(404) 879-2160 (Facsimile)

**Claims Appendix: Claims On Appeal**

16. A method for making a pharmaceutical composition comprising a porous matrix formed of at least one hydrophilic or hydrophobic excipient and microparticles of a drug, wherein the microparticles have a mean diameter between about 0.1 and 5  $\mu\text{m}$  and a total surface area greater than about 0.5  $\text{m}^2/\text{mL}$ , and wherein the dry porous matrix is in a dry powder form having a TAP density less than or equal to 1.0  $\text{g/mL}$  and having a total surface area of greater than or equal to 0.2  $\text{m}^2/\text{g}$ , comprising

- (a) dissolving a drug in a volatile solvent to form a drug solution,
- (b) combining at least one volatile solid pore forming agent with the drug solution to form an emulsion, suspension, or second solution,
- (c) incorporating at least one excipient into the emulsion, suspension, or second solution, wherein the excipient is selected from the group consisting of hydrophobic and hydrophilic excipients which enhance dissolution rate, which stabilize drug in amorphous form by preventing crystallization, and which stabilize drug in crystalline form by inhibiting crystal growth, and
- (d) removing the volatile solvent and pore forming agent from the emulsion, suspension, or second solution to yield the porous matrix of drug and excipient.

17. The method of claim 16 wherein step (d) is conducted using a process selected from spray drying, evaporation, fluid bed drying, lyophilization, vacuum drying, or a combination thereof.

18. The method of claim 16 wherein the excipients are selected from the group consisting of polymers, amino acids, wetting agents, sugars, preservatives, pegylated excipients, tonicity agents, and combinations thereof.

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19. The method of claim 16 wherein the matrix comprises between 1 and 95% drug by weight in combination with at least one hydrophilic or hydrophobic excipient which enhances the rate of drug dissolution, stabilizes the drug in crystalline form by inhibiting crystal growth or stabilizes the drug in amorphous form by preventing crystallization.

20. The method of claim 16 wherein the pore forming agent is a volatile salt.

21. The method of claim 20 wherein the volatile salt is selected from the group consisting of ammonium bicarbonate, ammonium acetate, ammonium chloride, ammonium benzoate, and mixtures thereof.

34. The method of claim 16, wherein the drug is selected from the group consisting of analgesics or antipyretics, antiasthmatics, anti-inflammatories, antimigraine agents, antiarthritic agents, anticonvulsants, antibacterial agents, antiviral agents, and antimicrobials.

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**Evidence Appendix**

1. Material Safety Data Sheet for PEG Telomer B
2. Definition of the term "volatile"

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**Related Proceedings Appendix**

None

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## SIGMA-ALDRICH

## Material Safety Data Sheet

Date Printed: 21/APR/2005

Date Updated: 16/MAR/2004

Version 1.1

According to 91/155/EEC

Classified as Hazardous according to the criteria of EU Annex 1 and NOHSC.

## 1 - Product and Company Information

Product Name ZONYL FSO-100 FLUOROSURFACTANT  
Product Number 421456  
Company Sigma-Aldrich Pty, Ltd  
Unit 2, 14 Anella Avenue  
Castle Hill NSW 1765  
Australia  
Technical Phone # +61 2 9841 0555  
Fax +61 2 9841 0500  
Emergency Phone # +61 2 9841 0566

## 2 - Composition/Information on Ingredients

Product Name	CAS #	EC no.	Annex I Index Number
PEG TELOMER B	None	None	None

## 3 - Hazards Identification

SPECIAL INDICATION OF HAZARDS TO HUMANS AND THE ENVIRONMENT  
May cause cancer. May cause heritable genetic damage.

## 4 - First Aid Measures

## AFTER INHALATION

If inhaled, remove to fresh air. If not breathing give artificial respiration. If breathing is difficult, give oxygen.

## AFTER INGESTION

If swallowed, wash out mouth with water provided person is conscious. Call a physician.

## 5 - Fire Fighting Measures

## EXTINGUISHING MEDIA

Suitable: Water spray. Carbon dioxide, dry chemical powder, or appropriate foam.

## SPECIAL RISKS

Specific Hazard(s): Emits toxic fumes under fire conditions.

## SPECIAL PROTECTIVE EQUIPMENT FOR FIREFIGHTERS

Wear self-contained breathing apparatus and protective clothing to prevent contact with skin and eyes.

## 6 - Accidental Release Measures

PERSONAL PRECAUTION PROCEDURES TO BE FOLLOWED IN CASE OF LEAK OR SPILL  
Evacuate area.

PROCEDURE(S) OF PERSONAL PRECAUTION(S)

Wear self-contained breathing apparatus, rubber boots, and heavy rubber gloves. Wear disposable coveralls and discard them after use.

METHODS FOR CLEANING UP

Cover with dry lime or soda ash, pick up, keep in a closed container, and hold for waste disposal. Ventilate area and wash spill site after material pickup is complete.

---

7 - Handling and Storage

HANDLING

Directions for Safe Handling: Do not breathe vapor. Avoid all contact. Do not get in eyes, on skin, on clothing. Avoid prolonged or repeated exposure.

STORAGE

Conditions of Storage: Keep tightly closed. Store in a cool dry place.

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8 - Exposure Controls / Personal Protection

ENGINEERING CONTROLS

Use only in a chemical fume hood. Safety shower and eye bath.

GENERAL HYGIENE MEASURES

Wash thoroughly after handling. Discard contaminated clothing and shoes.

PERSONAL PROTECTIVE EQUIPMENT

Special Protective Measures: Wear appropriate government approved respirator, chemical-resistant gloves, safety goggles, other protective clothing.

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9 - Physical and Chemical Properties

Appearance	N/A	
Property	Value	At Temperature or Pressure
pH	N/A	
BP/BP Range	200 °C	
MP/MP Range	N/A	
Flash Point	107 °C	Method: closed cup
Flammability	N/A	
Autoignition Temp	N/A	
Oxidizing Properties	N/A	
Explosive Properties	N/A	
Explosion Limits	N/A	
Vapor Pressure	N/A	
SG/Density	1.36 g/cm3	
Partition Coefficient	N/A	
Viscosity	N/A	
Vapor Density	N/A	
Saturated Vapor Conc.	N/A	
Evaporation Rate	N/A	
Bulk Density	N/A	
Decomposition Temp.	N/A	

Solvent Content	N/A
Water Content	N/A
Surface Tension	N/A
Conductivity	N/A
Miscellaneous Data	N/A
Solubility	N/A

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## 10 - Stability and Reactivity

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### STABILITY

Stable: Stable.

Materials to Avoid: Strong oxidizing agents.

### HAZARDOUS DECOMPOSITION PRODUCTS

Hazardous Decomposition Products: Carbon monoxide, Carbon dioxide.

### HAZARDOUS POLYMERIZATION

Hazardous Polymerization: Will not occur

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## 11 - Toxicological Information

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### SIGNS AND SYMPTOMS OF EXPOSURE

To the best of our knowledge, the chemical, physical, and toxicological properties have not been thoroughly investigated.

### ROUTE OF EXPOSURE

Multiple Routes: Harmful if swallowed, inhaled, or absorbed through skin. May cause irritation.

### TARGET ORGAN INFORMATION

Liver. Kidneys. Nerves.

### CHRONIC EXPOSURE - CARCINOGEN

Result: Carcinogen.

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## 12 - Ecological Information

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No data available.

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## 13 - Disposal Considerations

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### SUBSTANCE DISPOSAL

Dissolve or mix the material with a combustible solvent and burn in a chemical incinerator equipped with an afterburner and scrubber. Observe all federal, state, and local environmental regulations.

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## 14 - Transport Information

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### RID/ADR

Non-hazardous for road transport.

### IMDG

Non-hazardous for sea transport.

### IATA

Non-hazardous for air transport.

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## 15 - Regulatory Information

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### CLASSIFICATION AND LABELING ACCORDING TO EU DIRECTIVES

INDICATION OF DANGER: T

Toxic.

R-PHRASES: 45 46

May cause cancer. May cause heritable genetic damage.

S-PHRASES: 53 23 36/37/39 45

Avoid exposure - obtain special instructions before use. Do not breathe vapor. Wear suitable protective clothing, gloves, and eye/face protection. In case of accident or if you feel unwell, seek medical advice immediately (show the label where possible).

---

16 - Other Information

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DISCLAIMER

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define:volatile

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## Web

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### Definitions of **volatile** on the Web:

- evaporating readily at normal temperatures and pressures; "volatile oils"; "volatile solvents"
- explosive: liable to lead to sudden change or violence; "an explosive issue"; "a volatile situation with troops and rioters eager for a confrontation"
- fickle: marked by erratic changeableness in affections or attachments; "fickle friends"; "a flirt's volatile affections"
- tending to vary often or widely; "volatile stocks"; "volatile emotions"
- a volatile substance; a substance that changes readily from solid or liquid to a vapor; "it was heated to evaporate the volatiles"  
[wordnet.princeton.edu/perl/webwn](http://wordnet.princeton.edu/perl/webwn)
- Volatility is the standard deviation of the change in value of a financial instrument with a specific time horizon. It is often used to quantify the risk of the instrument over that time period. Volatility is typically expressed in annualized terms, and it may either be an absolute number (100\$ +- 5%) or a fraction of the initial value (100\$ +- 5%).  
[en.wikipedia.org/wiki/Volatility](http://en.wikipedia.org/wiki/Volatility)
- Smells of acetic acid and/or ethyl acetate, quite disagreeable when excessive though a tiny amount may enhance aromas.  
[www.sallys-place.com/beverages/wine/wine\\_glossary.htm](http://www.sallys-place.com/beverages/wine/wine_glossary.htm)
- Volatile means a material can evaporate. Volatility is the ability of a material to evaporate. The term volatile is commonly understood to mean that a material evaporates easily.  
[ccinfoweb.ccohs.ca/help/msds/msdstermse.html](http://ccinfoweb.ccohs.ca/help/msds/msdstermse.html)
- Any substance that evaporates readily.  
[www.epa.gov/OCEP/aterms/vterms.html](http://www.epa.gov/OCEP/aterms/vterms.html)
- Compounds with low melting temperatures, such as hydrogen, helium, water, ammonia, carbon dioxide and methane.  
[www.pgq.hawaii.edu/eschool/glossary.htm](http://www.pgq.hawaii.edu/eschool/glossary.htm)
- Pertaining to a readily vaporizable liquid that evaporates at a relatively low ambient temperature.  
[www.globalsecurity.org/wmd/library/policy/army/fm/3-6/3-6gl.htm](http://www.globalsecurity.org/wmd/library/policy/army/fm/3-6/3-6gl.htm)
- Slightly vinegary due to a high level of volatile (or acetic) acidity (VA). But a minimum level of VA often helps to clarify?? and project a wine's aromas without resulting in an unstable bottle. "High-toned" is jargon for faintly volatile, and is not necessarily pejorative.  
[www.wineaccess.com/expert/tanzer/glossary.html](http://www.wineaccess.com/expert/tanzer/glossary.html)
- Usually denotes a high level of acidity, alcohol and/or other flavor faults.



[www.quintadotodo.com/website/facts/glossary.html](http://www.quintadotodo.com/website/facts/glossary.html)

- most of the flavor components of wines are volatile, or easily perceivable by the nose. Volatile acidity refers to the acetic acid and ethyl acetate content of wines, their vinegary aspect.  
[wineschool.com/vocabulary.html](http://wineschool.com/vocabulary.html)
- A Java(TM) programming language keyword used in variable declarations that specifies that the variable is modified asynchronously by concurrently running threads.  
[safarixamples.informit.com/0201703939/More/JavaGlossary.html](http://safarixamples.informit.com/0201703939/More/JavaGlossary.html)
- refers to a liquid that changes to a gas at temperatures close to room temperature.  
[www.energyinst.org.uk/education/glossary/](http://www.energyinst.org.uk/education/glossary/)
- Subject to change. The volatile keyword informs the compiler that a variable could change value at any time (because it is mapped to a hardware register, or because it is shared with other, concurrent processes) and so should always be loaded before use.  
[biology.ncsa.uiuc.edu/library/SGI\\_bookshelves/SGI\\_Developer/books/DevDriver\\_PG/sgi\\_html/go01.html](http://biology.ncsa.uiuc.edu/library/SGI_bookshelves/SGI_Developer/books/DevDriver_PG/sgi_html/go01.html)
- Describes a substance that evaporates or vaporizes rapidly at room temperature, as a volatile liquid.  
[www.nalms.org/glossary/lkword\\_v.htm](http://www.nalms.org/glossary/lkword_v.htm)
- A chemical or substance that easily evaporates.  
[www.deq.state.or.us/wmc/cleanup/glossary.htm](http://www.deq.state.or.us/wmc/cleanup/glossary.htm)
- An attribute of a data object that indicates that the object is changeable beyond the control or detection of the compiler. Any expression referring to a volatile object, such as an assignment, is evaluated immediately.  
[www.absoft.com/Products/Compilers/C\\_C++/XLC/docs/glossary/czqv.htm](http://www.absoft.com/Products/Compilers/C_C++/XLC/docs/glossary/czqv.htm)
- A substance which evaporates easily is said to be 'volatile.' Things with a strong aroma are generally volatile, because the molecules easily pass into the surrounding air.  
[www.herbalchem.net/Glossary.htm](http://www.herbalchem.net/Glossary.htm)
- Volatile liquids change into vapour very easily, even well below their boiling point  
[www.uyseg.org/greener\\_industry/pages/glossary.htm](http://www.uyseg.org/greener_industry/pages/glossary.htm)
- subject to evaporation at a relatively low temperature.  
[www.sgia.org/glossary/Vv.cfm](http://www.sgia.org/glossary/Vv.cfm)
- Evaporating readily at normal temperatures.  
[www.scancliaspa.com/aromatherapy-glossary-terms.html](http://www.scancliaspa.com/aromatherapy-glossary-terms.html)
- used to describe the fluctuations in the price of a stock, bond or commodity.  
[www.mines.edu/stu\\_life/organ/mic/glossary.htm](http://www.mines.edu/stu_life/organ/mic/glossary.htm)
- A market which is often subject to wide price fluctuations is said to be volatile. This volatility is often due to a lack of liquidity. Lack of liquidity is caused by too few market participants, too little volume, or both.  
[www.tradingeducators.it/resources/glossary\\_t.htm](http://www.tradingeducators.it/resources/glossary_t.htm)
- The memory elements lose their contents when power is removed from the device. SRAM-based devices are volatile and require another device to store their configuration program.

[klabs.org/richcontent/Tutorial/PLD\\_Definitions.htm](http://klabs.org/richcontent/Tutorial/PLD_Definitions.htm)

- Refers to memory that is not saved when power is lost or turned off. See also nonvolatile.  
[www.intermec.com/eprise/main/Intermec/Content/About/GlossarySubpages/Glossary\\_UV](http://www.intermec.com/eprise/main/Intermec/Content/About/GlossarySubpages/Glossary_UV)
- Said of a wine with an excessive amount of volatile acidity. Wines with too much volatile acidity have an unpleasant, sharp vinegary aroma.  
[www.allhiwines.com/glossary.html](http://www.allhiwines.com/glossary.html)
- A wine affected by the presence of acetic acid is said to be volatile, or to have volatile acidity (va). In small amounts, this can contribute to complexity, but in excess it gives wine a slightly sour, vinegary edge.  
[www.southcorp.com.au/cps/rde/xchg/SID-53E7C3D8-BE21144E/southcorp/style.xsl/glossary.htm](http://www.southcorp.com.au/cps/rde/xchg/SID-53E7C3D8-BE21144E/southcorp/style.xsl/glossary.htm)
- Turning readily to a gas, or boiling easily  
[www.learnz.org.nz/steelmaking/glossary/index.php](http://www.learnz.org.nz/steelmaking/glossary/index.php)

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